centrifuged for a prolonged period of time and carefully stained, the presence of cocci will be demonstrable. Their presence will explain the fever and elevated pulse, which are usually out of proportion to the severity of the respiratory involvement. In such cases a careful physical examination will generally elicit a point of tenderness to palpation at the costomuscular angle, a finding which will leave the diagnosis beyond question. There are few conditions in which it is so difficult to correlate the clinical picture, the urinary findings, and the pathological conditions. The pathologist seldom sees kidneys of this type, for, fortunately, the condition is rarely fatal; and if it is, the pathologic changes have progressed far beyond those that were present at the onset of the condition. However, the numerous renal scars seen in the routine examination of autopsy materially attest to the accuracy of our clinical deductions.

Because the infection is principally in the cortex of the kidney, the urine does not contain any cellular elements, and investigation by intravenous urography will usually prove negative, as the infection does not produce abnormalities discoverable by these methods. Of considerable clinical importance is the regular early development of perinephritis, which produces the tenderness so characteristically found in the costomuscular angle.

With this group must be included the cases of pyelonephritis which are the result of focal infection. While the relationship between an abscessed tooth, infected tonsil, cervix or prostate is not as easily demonstrated either clinically or experimentally, the best opinion today seems to favor such a relationship. It may be possible as our knowledge advances we shall discover that these distant foci, instead of supplying the actual organisms that infect the kidney, produce a toxin which, by its chemical affinity for renal tissues, makes possible the continued growth of the infection either by neutralizing the natural immune processes, or so affecting the involved tissue as to make the site favorable for growth. Certainly, a careful review of experimental work along this line points in that direction.

(To be continued)

TISSUE CHANGES IN CHRONIC INTOXICATION OF BARBITALS*

By T. L. SCHULTE, M.D.
San Francisco

TISSUE changes have been reported several times in patients following acute fatal poisoning by barbital and its derivatives,[1-10] the main pathological changes being in the central nervous system, liver, kidneys, and skin. Somewhat similar changes have also been reported in experimental animals.[11-15] However, no one thus far has reproduced, experimentally, the dermatitis observed clinically in sensitive individuals using these compounds. In connection with another study, it was observed in this laboratory that dogs anesthetized repeatedly with pentobarbital developed a macular papular exanthem, accompanied by depilation, cracking and oozing, and resembling the clinical picture of barbital dermatitis. In the hope that this phenomenon might be reproduced which would permit an experimental study of the clinical manifestations of barbital idiosyncrasy, the following experiments were performed to study the phenomenon in more detail. In brief, there were carried out long-continued administrations to dogs and white rats of various members of the barbital group and histological examinations for possible alterations in skin and other organs.

PENTOBARBITAL AND AMYTAL IN DOGS

Pentobarbital.

Fifteen young adult dogs, fourteen males and one female, were used, three of the males serving as controls. The animals were fed a diet of commercially prepared dog food and water, and kept in the regular animal quarters. Food was withdrawn twice weekly for eighteen to twenty-four hours, then an intraperitoneal injection was given of pentobarbital† (sodium ethyl (methyl-propyl carbinyl) barbiturate), 50 milligrams per kilogram body weight, dissolved in three cubic centimeters of distilled water. Narcosis resulted in from thirty seconds to ten minutes and lasted from ten to twelve hours.

Four dogs died of intestinal perforation and peritonitis, following injection. Histologic examination of these animals showed cloudy swelling of the liver, kidney, spleen, and heart muscle, with septic infarcts and areas of necrosis in which bacilli were present. It is doubtful if these changes had any relationship to the effects of the drug. The remaining seven males developed patchy areas of depilation, and a macular papular erythematous exanthem of the entire body except the head, neck and saddle, in an average time of fifty days.

When the skin rashes appeared, an attempt was made to determine in each dog whether a specific dermal sensitivity was present which could be demonstrated by patch tests. Accordingly, the hair was shaved from the dorsolateral thorax bilaterally over an area 10 by 10 centimeters. Gauze squares, 3 by 3 centimeters, were saturated with solutions and applied to the shaved areas for twenty-four hours as follows: (1) pentobarbital in distilled water; (2) dog urine, obtained by catheterization of the bladder one hour after narcosis developed; and (3) distilled water. However, the patch tests were all negative in all the animals in the thirteen tests made.

The female dog developed ataxia of the hind legs after fifty days, and by the fifty-fifth day was completely ataxic, and had urinary incontinence. Sensation was normal as far as could be determined. However, these signs completely disappeared after the one-hundredth day. This animal became pregnant during the course of the experiment and gave birth to six pups. These were sacrificed when they were two weeks old; histologic examination of the skin and vital organs showed them to be normal.

Injections were continued over a period of two hundred days, during which time about sixty in-

* From the Department of Pharmacology, Stanford University School of Medicine, San Francisco.

† Supplied by Abbott Laboratories.

jections in each dog were made, and then the dogs were sacrificed. Histologic examinations of the skin, liver, kidney, spleen, and heart muscle showed them to be normal, in spite of the gross changes in the skin. The control animals showed no skin lesions on gross and microscopic examinations, and the vital organs were similarly normal.

Amytal.

To test the specificity of this dermatitis for pentobarbital, two other dogs were similarly injected with sodium amytal* (sodium isoamylethylbarbiturate), using 50 milligrams per kilogram body weight, for 250 days, at which time they were sacrificed. Gross observation throughout, and histologic examination of the skin and vital organs at necropsy, revealed only normal tissues.

There was a possibility that the skin lesions observed in the first dogs were infectious, or resulted from the manner of handling the animals. Accordingly, an entirely fresh stock of dogs was obtained that had no contact with the previous animals. Three young adult male dogs were used, one being injected with physiologic saline solution (0.85 per cent NaCl) as a control. Otherwise the procedure was similar to the first group of dogs, *i. e.*, treatment with pentobarbital, 50 milligrams per kilogram, injected intraperitoneally twice weekly. The special feature of the fresh group was that the animals were placed separately in clean, padded cages after the injections, and, while narcotized, were protected from trauma to the skin as much as possible. These animals developed no skin lesions, and so were sacrificed on the seventy-fifth day. Histologic examinations of the skin and vital organs showed them to be normal. Therefore, it appeared probable that the dermatitis observed in the first group of dogs was due to some intercurrent infection, or to trauma from scratching during the recovery period.

Different Barbitals in White Rats.

However, a further test of the possibility of producing dermatitis was made in white rats. Forty-five young adult females were used, housed five to each cage, and fed Purina Dog Chow. One cage of these rats was used as a control and given injections of one cubic centimeter per kilogram of saline solution; a second cage of controls was injected with paraldehyd 1.2 cubic centimeter per kilogram, as a check on the effect of a nonbarbital depressant, and the rats of the other seven cages received various barbital derivatives, as follows: sodium barbital (sodium diethylmalonylurea) 150 milligrams per kilogram, sodium phenobarbital (sodium phenylethylmalonylurea) 70 milligrams per kilogram, sodium amytal (sodium isoamylethylbarbiturate)* 50 milligrams per kilogram, pentobarbital (sodium ethyl (methylpropyl carbinyl) barbiturate)† 30 milligrams per kilogram, phandorn (2, 4, 6 trioxy-s-cyclo-hexenyl-ethyl-pyrimidin) 120 milligrams per kilogram, pentothal† 80 milligrams per kilogram, and sedormid (allyl-isopropyl acetyl carbamid) 100 milligrams per kilogram. The injections were made subcutaneously, three times a week for thirteen weeks, at which time the rats were sacrificed and the organs examined histologically. No skin lesions appeared at any time after these barbitals. Histologically, normal skin, liver, kidney, spleen, and heart muscle were present in all the barbitalized rats and the controls.

* Supplied by Eli Lilly & Company.
† Supplied by Abbott Laboratories.

COMMENT

The clinical reports in which necropsy revealed lesions in the liver and kidneys were in patients who had taken single massive doses of barbitals with suicidal intent. However, in some other similar cases no lesions in the liver and kidneys have been found. On the other hand, when a patient is sensitive to barbital or any of its derivatives, a single dose may be sufficient to cause a violent reaction. An exanthem following a single dose of phenobarbital has frequently been observed, and recently there has been reported thrombocytopenic purpura after the use of sedormid, apparently in sensitive patients.

The negative results in dogs and white rats obtained by me agree with those of Ravdin, Drobkin and Bothe,[11] Seevers and Tatum,[12] Holck and Kanan[13] and Swanson, Weaver and Chen.[15] The extensive dermatitis observed in the first group of dogs could not be reproduced under various conditions and, therefore, probably did not represent the same kind of dermal reaction seen clinically, but rather an intercurrent infection, or some manifestation of the experimental conditions other than the drug.

SUMMARY AND CONCLUSIONS

1. Skin lesions, manifested by depilation and a macular papular exanthem, were observed in seven dogs given pentobarbital intraperitoneally twice weekly for 205 days.

2. Repetition of this administration with pentobarbital and sodium amytal, in doses producing coma, did not furnish any histologic evidence of damage to the skin, liver, kidney, spleen, or heart muscle. Therefore, the skin lesions were probably due to scratching and purposeless movements made by the animals while emerging from narcosis, or they were infectious, since in other dogs placed separately into clean, padded cages following injection, no skin lesions developed.

3. Patch tests on these dogs, made with solutions of pentobarbital, urine and distilled water, gave negative results in thirteen experiments.

4. The following barbital derivatives or depressants injected subcutaneously into forty-five rats three times weekly over a period of ninety-one days, in doses producing coma, also caused no lesions in the skin, liver, kidneys, spleen and heart muscle, as determined by histologic examination: sodium barbital, sodium phenobarbital, sodium amytal, pentobarbital, phanodorn, pentothal, and sedormid. Control injections of paraldehyd and physiological saline solution also caused no pathological changes in the vital organs.

Department of Pharmacology,
Stanford University School of Medicine.

REFERENCES

1. Rivet, L., Jany, C., and Herbain, M.: Bull. et mem. Soc. Méd. d'hôp de Paris, 49:276, 1925.

2. Stalkind, E.: Lancet, 1:391, 1926.
3. Raun, J.: Hospitalstidente, 76:1103, 1933.
4. Gerloch, P., and Bredmose, C. U.: Hospitalstidente, 76:963, 1934.
5. Loewy, F. E.: Lancet, 1:845, 1934.
6. Carriere, G., and Huriez, C.: Presse Med., 43:465, 1935.
7. Birch, C. A.: Lancet, 1:478, 1936.
8. Ashworth, W. C.: South. Med. Surg., 98:592, 1936.
9. Hoffman, A. M., Kahn, J., and Fitzgibbon, J. P.: J. A. M. A., 110:725, 1938.
10. Moody, A. M.: J. A. M. A., 110:726, 1938.
11. Ravdin, I. S., Drabkin, D. L., and Bothe, A. E.: J. Lab. Clin. Med., 16:561, 1931.
12. Seevers, M. H., and Tatum, A. J.: J. Pharm. Exp. Therap., 42:217, 1931.
13. Holck, H. G. O., and Kanan, M. A.: J. Lab. Clin. Med., 19:1191, 1934.
14. Holck, H. G. O., and Cannon, P. R.: J. Pharm. Exp. Therap., 57:289, 1936.
15. Swanson, E. E., Weaver, M. M., and Chen, K. K.: Am. J. Med. Sc., 193:246, 1937.

VARICOSE VEINS IN PREGNANCY*

By A. M. McCausland, M.D.
Los Angeles

Discussion *by Nelson J. Howard, M.D., San Francisco; E. M. Lazard, M. D., Los Angeles; Lyle G. McNeile, M. D., Los Angeles.*

THIS is a preliminary report from the Los Angeles Maternity Service on the treatment of varicose veins complicating pregnancy.

This frequent complication predisposes to all degrees of invalidism throughout pregnancy as well as in later life. Their distressing symptoms and sequellae have been recognized for centuries. Unfortunately, as always, pregnant women, being the last to enjoy the benefits of medical and surgical advance, have been led to believe that varicose veins were part of the price of motherhood.

From the time of Ambrose Paré, in 1579, the injection treatment of varicose veins in pregnancy has been discouraged and condemned. The use of taping, bandages and elastic stockings was recommended, and afforded some temporary relief to the lower leg, but proved of little value in varicose veins of the vulva and upper thigh, where they are often extensive.

In 1931, Dr. H. O. McPheeters, in what was thought to be a daring article, urged the prophylactic injection treatment of varicose veins during pregnancy. This was based upon a series of cases treated in the Minneapolis General Hospital. Since his report, several clinics in this country and one in Great Britain have reported gratifying results. Many of the principles advocated by Doctor McPheeters are now followed at the Los Angeles Maternity Service.

REASONS FOR TREATING THE COMPLICATION

A few of the reasons for treating this complication are as follows:

1. To relieve the distressing symptoms and disabilities especially in women whose economic status is such that they must do their own housework.

2. To prevent thrombophlebitis. Dr. C. A. Nicholas reports that in one hundred patients treated at the Margaret Hague Maternity Hospital none developed postpartum thrombophlebitis. However, during the prenatal period three patients refused treatment for marked varicosities, and each of them developed thrombophlebitis.

3. To prevent the danger of excessive hemorrhage from the rupture of vulvar varicosities at the time of delivery.

4. To eradicate varicose veins which may persist throughout life. The cosmetic effect is gratifying to the patients.

5. To obtain better results: since there is usually some involution of the veins following parturition, the injection of the varicose veins during pregnancy aids in the establishment of a closer contact of the vein wall about the thrombus.

ANATOMY

To be considered are:

1. Great saphenous vein.
2. Small saphenous vein.
3. External pudendal.
4. Superficial circumflex iliac.
5. Superficial epigastric.

All of these veins—superficial, deep, and communicating—have valves with cusps facing upward and inward. These are usually in relation to a tributary vein and distal to it. The valves may have one, two, or three cusps, but most of them are bicuspid.

PHYSIOLOGY

Three factors influence the normal venous flow up the legs:

1. The action of the leg muscles. This is a systolic and diastolic action, and is especially effective in the deep venous system.

2. Negative intra-abdominal pressure produced by the raising of the diaphragm during expiration, which tends to aspirate the blood from the lower extremities. This also has a systolic and diastolic phase.

3. Competent valves which prevent back flow in the veins.

ETIOLOGY

Etiologic factors to be considered include:

1. Hormonal. This seems to be the most important single factor known at the present time.

2. Valvular defects. These may be of infectious or congenital origin.

3. Weakened vein walls with dilatation. These, likewise, may be of congenital or infectious origin.

4. Heredity.

5. Pressure theory. This is no longer accepted as an important factor, since varicose veins develop early in pregnancy. It may, however, be a factor late in pregnancy because of a reduction in the negative intra-abdominal pressure.

PATHOLOGY

The superficial venous system is more frequently involved because of the lack of supporting musculature, and the normal function is disturbed. This change in function may be due to the previously listed etiologic factors, and Bernstein, McPheeters, Kilbourne, Burger, Holder, and others have proved

* From the Department of Obstetrics and Gynecology, School of Medicine, University of Southern California, Los Angeles.

Read before the Obstetrics and Gynecology Section of the California Medical Association at the sixty-seventh annual session, Pasadena, May 9–12, 1938.